

5-1-1935

## Lymphatic leukemia

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LYMPHATIC LEUKEMIA

BY

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SENIOR THESIS

UNIVERSITY OF NEBRASKA

COLLEGE OF MEDICINE

1935

480666

The various blood dyscrasias have always fascinated me. More than a year ago, at the Douglas County Hospital, an autopsy-verified case of acute lymphatic leukemia which had previously been diagnosed as 1. bronchopneumonia, and 2. encephalitis lethargica, furthered my interest, and subsequently prompted me to make this rather comprehensive but far from exhaustive review of the literature on lymphatic leukemia.

#### DEFINITION

Leukemia is a systemic disease characterized by a hyperplasia of the leucocyt-producing tissues, and accompanied by a secondary disturbance of the composition of the blood, which manifests itself in alterations in the relative proportions of the leucocytes, the appearance of forms not normally found in the peripheral circulation, and usually by an increase in the total number of white cells. The disease may be divided into the chronic and the acute forms.

#### HISTORY

Our first knowledge of lymphatic leukemia dates from 1845 when Hughes Bennett (1) described the peculiar white appearance of the blood at autopsy, the massive enlargement of the spleen, and the presence of exceedingly large numbers of leucocytes in the blood. At this same time, David Craigie (2) described a case very similar to that of Bennett's, but his was more than likely a myelogenous leuk-

emia, because an enlargement of the lymph glands was not mentioned. Bennett's description failed to distinguish any qualitative change in the white blood cells from those of sepsis. Bennett says "Although the most evident lesion in life was enlargement of the spleen, I agree with Dr. Craigie in thinking that the immediate cause of death was owing to the presence of purulent matter in the blood, notwithstanding the absence of any recent inflammation or collection of pus in the tissues." "In the cavities of the heart and vena cava, the blood when removed was seen to have separated into a red or inferior portion, and a yellow or superior portion." And further, "----the following case seems to me particularly valuable, as it will serve to demonstrate the existence of true pus, formed universally within the vascular system." Concluding, Bennett makes the following statement. "When, then, we take into consideration the existence of these corpuscles thruout the vascular system, their general size and appearance, and, above all, the changes they underwent on adding water and acetic acid, there can be little doubt that they were true pus globules."

Virchow, who also described the disease in the same year, working independently of Bennett, described the disease as 'leukemia', while Bennett called it 'leucocythemia'. Virchow later made a distinction between 'splenic', in which splenomegaly was the chief symptom, and 'lymphatic', in which the lymph glands were chiefly affected.

Early classification was difficult, and for a time, an arbitrary figure of 50,000 leucocytes was the dividing line between leukemia and leucocytosis. The present day concep-

tion of diagnosis of the disease, which depends on the type of cell found in the blood and the tissues, rather than the total number of leucocytes, dates back to 1891, when Ehrlich succeeded in staining leukocytes, and classifying the varieties of the disease according to the type of cell; granular or nongranular.

The present point of view considers leukemia as consisting of several states, rather than a single disease picture, and so the term 'leukemic states' has arisen. All of these states, however, are consistent in showing histological evidence of leukemic hyperplasia, altho clinically and hematologically there may be extreme variation from the generally accepted picture of hyperleucocytosis, enlarged spleen, and lymphadenopathy. (3)

#### INCIDENCE

Lymphatic leukemia is relatively rare—an average of one case in every 2000 hospital admissions. It affects males about twice as often as females. This disease occurs at practically all ages, but is especially apt to occur in two certain periods. The chronic form is most prevalent at ages between forty-five and sixty, while the acute form has a decided preference for ages below twenty-five, and in this period the maximum incidence is in the first five years, falling sharply in the next five, but rising to a second maximum between the years of fifteen and twenty. It is doubtful whether all the cases reported in the age period from one to five are really acute leukemia, for at these

ages the blood response to various abnormal conditions, chiefly infections, is very marked, not only in the relative increase in certain types of white cells, notably lymphocytes, but also in the absolute number of leucocytes. (4)

While the above shows the common age periods, there are, of course exceptions. Cooke (5) reports a 'congenital' case in which the symptoms developed on the fourth day of life, death ensuing in twenty-three days. Cabot(6) reports a case of lymphatic leukemia in a man of seventy-six. Cooke (5) states that chronic lymphatic leukemia never occurs in children.

#### ETIOLOGY

The etiology of lymphatic leukemia is unknown. There has been a great deal of work done on this subject, and many theories propounded, but the two main theories considered at the present time are the tumor theory and the infective theory. The tumor theory is probably the most popular, and is based almost entirely on the changes which seem to be analogous with tumor formation, such as apparently purposeless proliferation of leucocytes, and their tendency to metastasize. However, "the newly formed cells are not in possession of resolving power which proper tumor cells possess and by which they entirely destroy the organs attacked." (7)(8)

Izaacs (18) summarizes the arguments in favor of the neoplastic theory as follows. "Some of the neoplastic characteristics of leukocytes in leukemia, are the uncontrolled growth, the tendency to form secondary foci of growth (metastases),

the progress to a fatal termination with cachexia, the neoplastic type of metabolic rate of the cells, the maturation with roentgen ray irradiation, the failure to transmit the disease by inoculation of human being with blood of affected patients, the absence of bacteriologic data of an etiologic nature, and the birth of perfectly normal children by leukemic mothers." The cells seem to have a different chromosome number from normal body cells, which may account for their altered growth potentialities.

E. Parks Weber (13), in considering the two theories, infective, and neoplastic, of leukemias, considers the disease, and all lymphadenoses in general, as malignant neoplasms which flare up, or are discovered at the time of, or shortly after an acute or chronic infection, just as carcinoma is at times. Three patients dying from carcinoma were inoculated by Shuffer 1905 with leukemic blood from another patient. None developed leukemia. However, perhaps a person suffering from a carcinoma, or malignant disease would not be susceptible to the virus. This is the only attempt that has ever been made to transmit the disease from man to man, and no one has succeeded in transmitting it from man to lower animals. (10)

The infective theory has some support from Woodman's survey of twenty-five cases, in which he found a focus of infection, pyorrhea, tonsillitis, sore throat, bronchitis, in eighty-two percent of his cases. Hill (9) reports several cases following extraction of teeth. Ellerman (8) has succeeded several times in inoculating healthy fowls

with a filtrate from leukemic fowls. The filtrate used, consisted of an emulsion of organisms passed thru the Berkefeld filter, and therefore cell free and microbe-free, for organisms up to the size of bacteria. The condition could then be transmitted from one bird to another easily, and indefinitely. This proves without a doubt that in the case of fowls, at least, leukemia is a definitely infective condition. Whether it is infective in humans or not is still a question, but "it would be hard to believe that a disease so similar in man and fowls could be induced by entirely different processes." (7) Furth (15) reports transmission of spontaneous leukemia in the fowl by injection of filtered blood and organ extracts, which suggests again that the causative agent may be an ultramicroscopic virus. Richter and MacDowell (16) transmitted leukemia very successfully in a highly inbred strain of grey mice, and they concluded by crossing experiments that the susceptibility to transmission is inherited as a Mendelian dominant character.(17)

Falconer (11) presents a case of benzol poisoning in which the patient recovered for a time, settling to a new and lower level of blood cell production, then passing, in the course of three years into a true, autopsy-varified status of lymphatic leukemia with fatal termination. This observation of Falconer's is not the only one of its kind, for several similar cases have been reported, and other cases, while not due to benzol, have apparently resulted from action of other chemicals and toxins. Arsenic has long been known to influence hemapoetic tissue. Falconer also suggests that



while his case gives no definite proof that benzol causes lymphatic leukemia, it may act as an irritant and destructive agent to the hemapoetic system, upsetting the balance between lymphocytic production and destruction, resulting in lymphatic leukemia. Lignac (12 quoted from Falconer 11), in 1928, reported the results of injecting mice with from twenty-five to thirty injections of benzol (0.1 c.c. of 0.3% benzol in 10 c.c. of olive oil). He concluded: "All the symptoms of hyperplasia developed. After a time, the spleen, which was at first hypertrophied, decreased in size. No animals showed lymphatic leukemia, only hyperplasia. Up to the present time, I have not succeeded in producing lymphatic leukemia."

McGauran (12) reports three cases of leukemia in one family. Two were of lymphatic, and one of myelogenous type. He also mentions other questionable descriptions of two or more in one family. Cooke (5) speaks of a congenital case; in which the first symptoms were noted on the fourth day of life, and death in twenty-three days. There was a typical clinical and blood picture of acute lymphatic leukemia. He also mentions two other cases in very small infants, one appearing ten days after birth and dying three months later, and the other appearing in three months of age, death ensuing at the age of six months. Russel (19) reports a case of chronic lymphatic leukemia in which pregnancy occurred, and a live baby was born six weeks before the woman died. The blood count of the baby at six weeks of age was as follows: red cells, 3,610,000; white cells, 17,600; hemaglobin, 17%.

lymphoblasts, 5; large lymphocytes, 21; small lymphocytes, 27; medium lymphocytes, 29; metamyelocytes, 6; mature neutrophils, 10; eosinophils, 2. One lymphoblast with mitotic division was noted. In way of explanation, Russel says, "Since the fetal and maternal blood cells are completely separated, it is obvious that these abnormal and immature lymphoblasts and lymphocytes were formed in the infant. That these cells subsequently disappeared, suggests they were the response to a maternal influence rather than a fixed character of the infant. It is also interesting to note that in the mother's blood mitotic figures were very numerous during the last ten days of life, and numbered one mitosis in every 500 white blood cells."

#### SYMPTOMS

In the chronic forms, the disease begins so gradually that its exact time of onset can rarely be determined accurately. The accidental discovery of one or more painless swellings, or enlargement of the tonsils may be the first cause of the patient's seeking medical advice. In other instances the individual may complain first of increasing weakness and loss of weight, and it is the physician who discovers the anemia with enlargement of lymph glands and spleen. In cases where the anemia is of considerable grade, some of the characteristic secondary symptoms may be found, such as dyspnea, cough, palpitation, swelling of the ankles, headache, vertigo, tinnitus, general lassitude, and gastrointestinal disturbances, none of which is in any way diag-

nostic of the disease. Hemorrhages into the skin, or from the nose, bowel, lung, and gastro-intestinal tract may occur, but are decidedly more often seen in acute types of the disease. (20)

The onset of acute lymphatic leukemia is much more sudden. Not infrequently, following such infections as tonsillitis, a furuncle, or an abscessed tooth, the patient is suddenly taken ill with high fever, headache, general malaise, and extreme prostration. The gums frequently are red, swollen and spongy, reminding one of scurvy. There is a marked tendency to hemorrhage. The tonsils are often much enlarged, and may share in necrotic or gangrenous processes in the mouth. The regional lymph glands of the jaw and neck enlarge rapidly. The picture is so similar to that of an ordinary infection, that the true nature of the process is unrecognized, and incision of such glands has been made for drainage. The pallor which is present as a rule, and the swollen gums should arouse suspicion of a leukemic process, and suggest a differential blood count. The white count is usually subleukemic in the early stages. All of the above symptoms may not be present in every case. Thus there may be the following types; 1. severe or ulcerative gangrenous processes in the mouth, accompanied by minimal hemorrhagic tendency with little lymph gland or splenic enlargement. 2. Cases in which the hemorrhagic diathesis is the most striking feature suggesting the symptom complex-purpura hemorrhagica with hemorrhage into skin and mucous membrane. 3. Cases of a less virulent type where lymph node swelling,

and splenic enlargement are the salient features. 4. Occasional rare instances where none of the foregoing symptoms are present, but only a fever and high degree of anemia are evident. Before death, however, there usually occurs some evidence of ulceration in the mouth, of the hemorrhagic diathesis, or of involvement of lymph glands and spleen. (20) Izaacs (18) sums up the symptomatology thus: "The first symptom of leukemia is ease of fatigue. The symptoms as a whole, fall into four groups; those associated with an increase in basal metabolic rate (nervousness, abnormal perspiration, loss of weight); those associated with enlarged organs and glands (pressure symptoms, pains, cough, diarrhea, constipation, frequency of urination, and similar symptoms on the part of any organ the function of which is disturbed because of the abnormal growth); symptoms associated with anemia and myocardial insufficiency (dyspnea, edema, fatigue); symptoms associated with abnormal metabolism following the gradual process of the disease (cachexia). The progressive anemia, and in lymphatic and acute leukemias, the blood platelet deficiency are the result of the crowding out of the formative cells by the leukemic tissue." Cooke (5) in his recent survey of fifty cases of acute lymphatic leukemia in children, lists the six most common symptoms he found, in the following order. 1. Asthenia--in those complaining of weakness and pallor. 2. Dyspnea--due to pressure of leukemic tumors in the mediastinum--may also give cyanosis of the neck and face. 3. Rheumatoid pains. 4. Cervical adenopathy. 5. Abdominal pain--"Some have definite symptoms of peritoneal irritation, with spasm, vomiting, etc. 6. Stomatitis--not very common.

The most common symptoms have been named above, and those symptoms are quite constant in the so-called typical cases. However, in the atypical cases, the symptomatology may be extremely bizarre, owing to the fact that the pathological changes may be found in practically every organ of the body. There are those patients in which changes in the nervous system, gastro-intestinal tract, osseous system, joints, skin, etc., may play the most prominent part in the symptomatology, and so obscure the real nature of the illness until a routine blood count may be made, or sometimes, a correct diagnosis may be made only at autopsy.

#### PHYSICAL EXAMINATION

Physical examination is, in the typical case of chronic lymphatic leukemia, of great value. It usually reveals pallor, general glandular enlargement, enlarged spleen, at least to percussion, and an enlarged liver. There is usually a loss of weight.

The eyes are usually negative on physical examination, but are sometimes affected. Occasionally the fundus may show 'retinitis leukemica', small white flecks with a red border, a peculiar type of hemorrhage, and blurring of the optic disc.

The ears are rarely affected. Occasionally deafness may occur due to lymphomatous involvement of the labyrinth. Fioretti (quoted from Ordway and Gorham (3)) has reported a case of chronic leukemia with otitis media and deafness.

The upper respiratory passages are rarely affected in

chronic cases. However, ulcers are occasionally seen in the glottis, epiglottis, larynx, sinuses. Newton (21) cites a case of his in which the primary symptoms were in the throat, long before any other symptoms or before the blood picture was significant.

Swelling and bleeding of the gums leading to gangrenous processes in the mouth and pharynx may occur occasionally, but are much more frequently seen in the acute cases.

The tonsils are often enlarged, and may be the first symptom bringing the patient to seek medical advice.

Involvement of the thymus is not common. (22)(23).

The lymph gland enlargement is the most characteristic feature of the disease and is nearly always present, at least at some stage in the disease. Cervical, axillary, and inguinal glands are most frequently involved, and vary in size from a pea to a walnut and even larger. These glands are usually not inflamed, and usually exist in chains, separately, freely moveable, not attached to the skin, and not showing redness. Of course if there is an upper respiratory infection also, the cervical glands may be tender, reddened, and the picture entirely changed. Lyday's case (24) of co-existing tuberculous adenitis and lymphatic leukemia necessarily changed this picture.

In the heart there are no signs specific of leukemia, but as the anemia progresses, myocardial insufficiency may develop. Mitral insufficiency may be seen, also due to the progressing anemia.

Pleural effusion may occur, possibly due to infiltration of mediastinal lymph nodes.

The liver can usually be felt, its firm, smooth edge extending from one to four finger's breadths below the costal margin. It may occasionally be enormous, extending below the umbilicus.

Enlargement of the spleen is present in almost every case, and in some cases may fill the whole left side of the abdomen and past the umbilicus to the right. It is smooth, non-tender and firm.

The gastro-intestinal tract is often involved, giving varying degrees of anorexia, flatulence, nausea, vomiting, hematemesis, constipation, and diarrhea. Bloody stools may occur, but these are probably due to the hemorrhagic diathesis rather than actual leukemic infiltrations.

The kidneys show nothing peculiar to leukemia. There is often a mild albuminuria, which is probably a fever reaction.

The sexual organs are sometimes affected. In the female, menstrual irregularities with increased or decreased flow may occur. Priapism is uncommon, but not rare in the male. It has also been reported in the female.

Involvement of the central nervous system is quite common and will be discussed under 'Pathology'.

Lesions of the skin are common, and consist of pruritis, prurigo, localized infiltration, nodules, vesicles, pustules, urticaria, bronzing, tumors, petichia, papules, and hematomas. Leukemia cutis has been reported by Sweitzer, in which the whole skin was affected, being thicker than normal.

Tumor-like nodules or infiltrations have been reported occurring about the orbits, ribs, and sternum. Bone tenderness may sometimes be elicited.

In the acute lymphatic leukemias, the physical examination shows quite a different picture. One of a terrific fulminating character. As a rule the patients look very ill, and pallor is noticeable. Hemorrhages in the fundus of the eye are common. The most frequent involvement of the ear is deafness with Menieres syndrome. Palsy of cranial nerves may occur, and cerebral hemorrhage is not uncommon. The most characteristic lesions are in the mouth, where the leukemic process often leads to swelling, ulceration, and gangrene of the gums, cheek, pharynx, and tonsils. Noma may be the result of the necrotic process. Lymphadenopathy is nearly always present in the cervical region, but is not nearly as constant in other glands as in the chronic form. There is a high fever, and petechia, purpura, nodules, and occasional areas of necrosis are seen. Enlargement of the spleen and liver are usual, but these organs don't show the massive enlargement as seen in the chronic forms. Vomiting, diarrhea, and hemorrhage from the bowel may be seen. (3)

#### CASES

While I have already described symptoms and physical findings, I think these may be brought out perhaps a little more vividly by the citation of two cases. Both of these cases were chosen because they represent what might be called more or less typical cases; the first being a chronic and the second an acute case of lymphatic leukemia. Due to the fact that I have not been able to observe a case while



this paper was being written, I shall quote from Jaffe (25), and Park (26) these two case reports.

Case I: "A white man, age 57, was admitted to the hospital stating that he had lost 50 pounds in weight during the past eight months. He also had noted an enlargement of lymph nodes and complained of severe pains in the arches of his feet. Shortly prior to his admission he had a severe attack of sore throat. On admission, the temperature was 98F.; the pulse rate was 120, and the respiratory rate was 24. The blood pressure was 158/87. The anterior and posterior cervical lymph nodes and the sub-mandibular, inguinal and axillary nodes were pea sized, soft, discrete, and painless. The lower pole of the spleen could be palpated five fingerbreadths below the costal arch, and the lower border of the liver was felt  $2\frac{1}{2}$  fingerbreadths below the costal arch. The erythrocyte count was 3,250,000, hemaglobin 60%, leucocytes 139,000, with lymphocytes (about one and one half times normal size with coarsely trabeculated nuclei, and narrow rims of deeply basophilic cytoplasm) 98%, and lymphoblasts (three times the size of lymphocytes) 2%. Under treatment with benzene, the lymph nodes and spleen became smaller, and the white cell count dropped to 98,000. The lymphocytes diminished to 95%, and two polys were found. In the fifth week of the patient's stay in the hospital, he suddenly began to have severe pain in the region of the spleen, and the temperature rose to 102F. Two days prior to this attack, he had a sore throat. He became rapidly weak, and died four days after the onset of the abdominal pain."

Case II: "W.C., a boy of six years, from Boytown, Texas, was admitted to Hermann Hospital, at 7:00 P.M., May 8, 1930 in a state of coma. The temperature was 101.8F by rectum, pulse 106, respiration 46. He was delivered at full time, and was apparently normal at birth. There was nothing unusual in his feeding history. The past history was negative save for mumps at two years of age. The child was apparently well until three days before admission to the hospital, when he complained of feeling tired and wouldn't play. He was given 2 gr. of calomel followed by castor oil, during the next two days. There was no improvement in his condition, so a physician was called. At that time his abdomen was noticeably enlarged, and he complained of generalized abdominal pain. Quinine treatment was instituted on the belief that the child had malaria because of the large spleen. His condition became progressively worse, and at noon of May 8, 1930, he became unconscious and remained so. The illness was not ushered in by a chill, nor was there any gastro-intestinal disturbance until after admission into the hospital, when he vomited bile and wretched continuously. Pain in the abdomen, constipation, fever, loss of appetite, and stupor were the outstanding features prior to the admission to the hospital.

Physical examination revealed a well nourished child of about stated age, in a state of coma. The pupils were equal and reacted to light and accommodation. The ear drums were normal. The nose and throat revealed no abnormalities. The teeth were in fairly good condition. The tongue was dry

and coated. The mucous membrane of the mouth was dry and pale. Chest expansion was equal and normal. Respiratory rate 46. The lungs revealed no dullness, but there was broncho-vesicular breathing over both lobes. Pulse rates were equal, regular, and full; rate 106. No heart murmurs were present. The apex beat was in the midline in the fourth interspace. There was slight cardiac enlargement to the right. Blood pressure was 114/40. The abdomen was markedly distended and tympanitic-no fluid was demonstrable. There were no superficial scars present. The spleen was palpated five fingerbreadths below the left costal margin, reaching to the midline anteriorly, and the posterior axillary line posteriorly. The liver border extended four fingerbreadths below the right costal margin, blending with the splenic tumor anteriorly. The liver and spleen were smooth with firm edges. The genitalia were negative. Rectal examination was negative. The skin was dry and palid. There was not a general enlargement of superficial lymph nodes. The superficial reflexes were dulled. The patient's condition became rapidly worse, death occurring at midnight, at which time the rectal temperature was 106.2F. The urine showed a one plus albumen, and a trace of acetone. The blood count was as follows: Hemaglobin 40%, erythrocytes 2,600,000, leucocytes 304,000, lymphocytes 88, polys 2, and degenerative forms 10."

## BLOOD PICTURE

To more thoroughly understand the pathological processes in the leukemias, it may be helpful to briefly summarize the current views concerning the origin of the leucocytes. Although this paper is concerned only with lymphatic leukemia, it is almost necessary to know something of the origin of all the leucocytes, since they are so closely related.

The controversy concerning the origin of leucocytes turns on the question as to whether the several types of leucocytes can be traced back to a common ancestor form, a primitive leucocytic stem cell, or not. Three main groups of leucocytes are recognized, the granular leucocytes, the monocytes, and the lymphocytes. Pepper and Farley (27) are of the opinion that these groups not only arise from different mother cells, but also from different sites.

THE GRANULAR LEUCOCYTES: At first these cells are found only in the apparently extravascular areas, but soon they can be seen pushing their way between the lining endothelium of the vascular channels to enter the circulation. In the human adult, these cells have their chief, if not their only site of origin in the active or red bone marrow. However, there is some evidence that the eosinophils or basophils, which are members of this group of granular leucocytes may also arise outside the bone marrow. From its usual marrow origin, the name given to the early forms of this group, the myeloblasts and myelocytes is derived. The most immature of this

group of cells to appear in the peripheral circulation is the myeloblast, but this appears only under definitely abnormal conditions. Myeloblasts have not yet acquired their granules. The myelocyte is the name of the cell which occurs half way between the myeloblast and the mature leucocyte. This cell looks like the myeloblast, except the granules have appeared. These granules may be neutrophilic, eosinophilic, or basophilic, depending on which stain they take. Many workers have attempted to name the intermediate forms between the myeloblast and mature leucocyte with such terms as 'premyelocyte', and 'metamyelocyte', but these names have not been widely used. In normal blood, both young and old granular leucocytes are present with one or another of the specific granulations named above. The youngest still have the one large nucleus, but as the cells grow older, the nucleus becomes more and more indented and lobulated, "finally dying of senility". These are called polymorphonuclear leucocytes.

MONOCYTES: These cells are said to arise from reticulo-endothelium, or vascular endothelium, or even from connective tissue cells. Forkner (28) says, "Apparently from reticulo-endothelium there may, by proliferation, be produced either the monocytes of the blood, or analagous extravascular forms, the so called 'classmocytes' of the connective tissue". The mature monocyte is a large round cell with a large, round, indented or kidney-shaped nucleus.

LYMPHOCYTES: Now we come to the group of leucocytes with which this paper is chiefly concerned, the lymphocytes.

They arise from any of the lymphoid tissues of the body, even in small measure from that contained within the bone marrow itself. Groups of lymphocytes are present in the follicles of all lymph nodes and in the follicles of the spleen. The origin is therefore in sharp contrast to that of the granular leucocytes and monocytes. Lymphocytes in the blood are of variable size and appearance, the smaller ones being little larger than an erythrocyte, and have a deeply staining nucleus and little cytoplasm. The larger forms approach the monocyte in size, and have a larger, less deeply staining nucleus and more cytoplasm. It is a question which of the two forms is the more mature. Since it is the larger form that appears in preponderance in measles, small pox, and lymphatic leukemia, it would seem that they are the less mature. The youngest form, namely the lymphoblast appears in the peripheral blood only under definitely abnormal conditions. This cell closely resembles the myeloblast, and it is because of this similarity that some authors believe them to be the same cell, and precursors of all the leucocytes.

**ERYTHROCYTES:** These are the red blood cells, and are formed from erythroblasts in the bone marrow. The erythroblasts or normoblasts, the immature cells, are found in the peripheral blood only in severe anemias. This is mentioned merely because normoblasts are often seen in the blood of far advanced cases of leukemia due to the usual marked anemia.

**THROMBOCYTE:** This is the last formed element of the blood, also known as the blood platelet, and is said to arise from

the giant cells or megacaryocytes in the bone marrow, and they are mentioned here because their decrease is intimately associated with the purpura nearly always seen in terminal stages of the leukemias.

The blood picture is the only definite diagnostic finding in the leukemias. In the chronic form, the gross appearance of the fresh blood is not remarkable except that it may be pale, varying with the degree of anemia. The erythrocytes are slightly, or not at all reduced in the early stages, but the average count when the patient is first seen is under three million, which falls to a lower figure as death approaches. The occurrence of a remission is accompanied by a rapid rise in the erythrocytes sometimes even to normal values. The hemoglobin count tends to parallel the red cells, and the color index is low as a rule. The number of leucocytes per cubic mm. of blood is according to Cabot's figures, 180,000. (29) Cases with higher counts are seen, however, though rarely exceeding 1,000,000. The blood platelets are decreased, and Minot and Buchman (30) state that this is a characteristic feature of the disease. It is believed by some to be due to a crowding out of their parent cells (megakaryocytes) from the marrow by the hyperplasia of lymphoid elements. Persistent thrombopenia may exist for a long time before death, so that it cannot be in itself an indication of approaching death.

The stained blood film, when the disease is advanced, shows changes in the red cells of a severe secondary anemia. There occur nucleated red cells, normoblasts, more rarely

megaloblasts, anisocytosis, poikilocytosis, megalocytosis, polychromasia, and basophilic stippling. The appearance of white cells is that of striking uniformity. The great majority of them, that is, 95% to 99% are seen to be practically identical with the small lymphocyte of normal blood. The extreme fragility of many of these pathological lymphocytes is shown by the protoplasmic masses in the smear, sometimes called 'basket cells'. Shilling (31) has the following to say, " The blood picture is very uniform, with small lymphocytes predominating. There is often, but not always, a high leucocytosis (to above 1,000,000). The lymphocytes present are partly atypically large, with lobulated nucleus, or else they show very young pale nuclei with one or two nucleoli (lymphoblasts); the protoplasm may be abundant, or at times barely visible. Crushed forms are frequent nuclear shadows. The more acute the course, the more macrolymphocytic the blood picture. There are exceptions to this finding. In pronounced anemia there is also polychromasia and normoblasts; perhaps a megalocytic blood picture. There is a negative oxydase reaction of all oxydase cells. In lymphatic leukemia with anemia, the admixture of occasional myelogenous elements (myelocytes, juveniles, normoblasts) is not rare; the presence of great numbers of lymphocytes practically always determines the diagnosis. Blood platelets are usually decreased--a true thrombopenia. " Izaacs (18) says, " All leukemic patients, if they live long enough, end up in the ' blast ' stage, that is, the cells appear in less and less mature stages in the blood stream, and more immature forms are seen in greater numbers in blood forming organs."



As to the red cells, hemaglobin, and platelets, Rosenthal and Harris (32) in a recent article have the following to say, " The hemaglobin and the number of erythrocytes are usually reduced in acute leukemias. In chronic types, anemia may be absent or only moderate at the onset. The anemia is hypochromatic with a color index that varies from 0.5 to 1. Nucleated red cells are usually present. The blood platelets present marked variations in leukemia. In the early stages of a chronic leukemia they are normal, but they are usually profoundly reduced in acute varieties or in acute exacerbations of the chronic form."

The blood picture in acute lymphatic leukemia is very similar to that of acute myelogenous leukemia. There is usually a marked anemia with a rapid and progressive fall of the total red cell count and hemaglobin content. Variations in size shape, and staining reaction of the red cells is frequent. In the severe cases, basophilic granulation, normoblasts, and megaloblasts may be found. The resemblance to pernicious anemia may be marked. In the early stages, the white blood count may be, in fact, is usually subleukemic, ranging from a few thousand up to 30,000. In some instances, the count rises rapidly from day to day, amounting to several hundred thousand, but on the average, the numbers do not reach such great heights as in the chronic form. The blood platelets, as a rule are markedly reduced, and this reduction is progressive thruout the disease, explaining the tendency to hemorrhage late in the course of the disease. The percentage of lymphocytes range from fifty to ninety or above, and

in the acute form, the large lymphocyte predominates. Myelocytes are rarely seen and when present, represent a stimulation myelocytosis. They tend to disappear as the disease progresses.

In Cooke's (5) report of fifty cases in children, of which forty-five were acute lymphatic type, the polys averaged 1% to 15%. Myelocytes were rarely found. The remainder were small lymphocytes. (Ordway and Gorham (3) found a great preponderance of large lymphocytes in the acute cases.) The total leucocyte counts varied from 250 to 815,000. There was also great variation in individual patients in the white cell count. In one case the leucocytes dropped from 200,000 to 5,000 in three days without treatment.

Dimmel (33) observed that the histologic changes in acute leukemia are similar to those in the chronic form, and the predominating hematalogic features are the quite immature and degenerated cells.

The forgoing description of blood picture is that of the so-called typical case of chronic or acute lymphatic leukemia. However, many cases have been reported in which the blood findings were quite different. Abnormally low total leucocyte counts may persist thruout the course of the disease, and if verified by repeated observations, and autopsy findings may be designated as aleukemic leukemia.

Shilling (31) recognizes the existence of these conditions which clinically are leukemias, but microscopical study of the blood shows normal or subleukemic picture. He states that they may be temporary, or may change into manifest

leukemias. Aleukemic types are most often of the lymphatic type. Pinkerton (34) says, " Atypical conditions are frequently encountered that clinically and pathologically appear to be borderline cases showing various mixtures of the characteristics of acute infections, the purpuras, the anemias, and the neoplasms of the blood. The term aleukemic leukemia is commonly applied to an ill-defined group of cases in which the blood picture during life shows severe anemia, but does not justify the diagnosis of leukemia, while at autopsy, in addition to the leukemic-like cellularity of the bone marrow, accumulations of the myeloid or lymphoid cells are found in the viscera, these accumulations having a qualitative, but usually not a quantitative similarity to those true leukemias." Pinkerton is also of the opinion that autopsy findings are necessary to clinch the diagnosis of leukemia in many atypical cases. Kracke and Garver (40) say, " The term ' aleukemia ' is misleading. The condition probably should be considered a leukopenic stage of the existing leukemic process. The reasons for disappearance of leucocytes in the peripheral blood is shrouded in mystery. This phase may occur at any stage of the disease."

Asseltine (35) reports a case of lymphatic leukemia which he followed for one year in which the blood picture was aleukemic thruout the course of the disease, altho the last blood count was done one month before death. It is quite probable that if another count had been made a day or two before death occurred, the total white count would be found to be increased. However, it serves well to illustrate the

chronic aleukemic lymphatic leukemia. The first differential blood count was made four months after the onset of symptoms of fatigue and shortness of breath. This showed; hemaglobin 45%, red cells 2,560,000, white cells 4,350, polys 28, metamyelocytes 30, eosinophils 4, basophils  $\frac{1}{2}$ , and large lymphocytes  $3\frac{1}{2}$ , small lymphocytes 8, monocytes  $\frac{1}{2}$ , and mast cells  $24\frac{1}{2}$ . The total white cell count remained about the same, being 6,600 one month before death. However, the differential count changed completely, being at one month before death--polys 2%, and small lymphocytes 98% (of which 30% were immature). This picture is of interest because there was a moderate leucopenia thruout, and because the differential suggested myelogenous leukemia early in the disease, but was definitely lymphatic in the terminal stages.

Harvey (36) reports a case which was definitely lymphatic leukemia as shown by autopsy, but which showed a leucopenia thruout, the leucocytes ranging from 760 to 6,000 (terminal). The lymphocytes, however, were great in number, characteristic of lymphatic leukemia. Cooke (5) mentions a case in which the white cells reached the low figure of 250. Bowcock and Bishop present a case (37) in which the white count was 2,650 when the patient was first seen. Two months later it rose to 70,000, but suddenly dropped to 10,000 to 14,000, remaining so until just before death. At the onset, the differential count was practically normal--36 lymphocytes. Near the time of death, the lymphocytes were 85%, most of the large, immature type. Smith (38) reports a peculiar case in which for the first twelve days of hospitalization the white

cell count ranged from 3,100 to 600, and from then until death thirteen days later, ranged from 600 to 57,650. The lymphocytes ranged from 51% to 97%. Weber and Weisswang (39) speak of a case which when first seen had a blood count of 6,000 white cells and 79% lymphocytes, but  $2\frac{1}{2}$  months later had 36,100 white cells with 79% lymphocytes.

So we see from studying these cases of autopsy-verified leukemia which during life showed low or even leucopenic blood pictures, that the diagnosis of lymphatic leukemia does not rest on the presence of a high total leucocytosis, but rather on the presence in the peripheral blood stream of large numbers of lymphocytes, ranging from 80% to 99%, and the occasional presence of immature forms, lymphoblasts.

#### DIFFERENTIAL DIAGNOSIS

The diagnosis of the typical acute or chronic lymphatic leukemia is usually easy, but as already has been mentioned, many of the cases are not at all typical, and in those cases, differential diagnosis may become extremely difficult, definite diagnosis sometimes being impossible without conclusive autopsy findings.

Krumbhaar (41) reports several cases of other diseases which were confused with leukemia. In one case, a girl of three years had measles, and later developed whooping cough. A routine blood count showed 71,600 white cells of which 82% were lymphocytes (mature forms). Three months later a blood count showed 13,700 leucocytes with 42% lymphocytes. He also cites two other cases; one by Bourne and Scott (42) in which a boy with whooping cough had a white count of 176,000,

(66% lymphocytes) and one by Cabot (43) with 94,000 white cells (75% lymphocytes). It is well known that acute infections occurring in the course of lymphatic leukemia will often produce a tremendous rise in the leucocytes. (41, 43, 44, and others) It may also be mentioned that certain acute infections will produce a leukemoid-like blood picture.

Krumbhaar mentions a case of a woman who delivered a normal child, and three days later ran a temperature of 102-104 F., and had a leucocytosis of 7,600 with 75% lymphocytes. Another woman suffering from cancer of the breast and hemorrhage, showed a white count of 120,000, all polys. Still another of his cases, one of septicemia showed a leucocyte count of 112,300 with 85% polys.

Cooke (44) reports a case which showed an atypical symptomatology. The child, eleven years of age, showed no symptoms except vomiting once a day for six days, and then suddenly died. He was active, and went to school up to two days before he died. Brain hemorrhage was the cause of the vomiting. Autopsy also showed extensive infiltration of other organs.

Fries (45) reports a case of symptomatic thrombocytopenic purpura complicating leukopenic medullary lymphatic leukemia in which the blood picture was very confusing. There was never a leucocytosis of over 15,000 until just before death, altho the lymphocytes numbered as high as 75%. She says, " As the spleen showed no pathological lesions of lymphatic leukemia, and as there was no lymphadenopathy, one must consider the seat of the disease to be present

solely in the bone marrow."

Goldman (46) mentions an interesting case--one of chicken pox with a blood picture of lymphatic leukemia. The white count was 81,200, polys 7, and lymphocytes 86. The lymphocytes, however, were all small type, there usually being some large immature cells in acute leukemias in children. This picture remained about the same for two weeks; then returned to normal. There were never any symptoms of leukemia or whooping cough. The chicken pox lesions seemed to persist longer than usual.

Smith (38) calls attention to the fact that atypical lymphatic leukemia may be confused with aplastic anemia and agranulocytic angina. One of his cases showed blood counts at various times similar to both of the diseases. " At one time, 14 days after admission to the hospital, there was a picture of aplastic anemia; white cells 600, red cells 1,500,000, hemaglobin 40%, lymphocytes 57%, polys 36%, and platelets 34,760. The red cells showed anisocytosis, poikilocytosis, and occasional normoblasts." " At another time, clinical and laboratory findings showed a typical agranulocytic angina. There were white necrotic patches on both tonsils; and leucocytes numbered 2,560, red cells were 2,650,000, polys 30, and lymphocytes 69%. The throat became very red and swollen, and then gradually subsided". Weber and Weiswange (39) also showed a case in a boy that showed a clinical picture, at the onset, of hypoplastic anemia with palor, anemia, and epistaxis. Rothrock (47) reports a case of agranulocytic angina in which clinically it was typical, and

there was a granulocytopenia. However, at autopsy, it was proven to be a chronic lymphatic leukemia. This is confusing, to have the blood picture and autopsy findings of a chronic lymphatic leukemia and the clinical picture of agranulocytic angina, a very acute condition. Therefore, Rothrock likes to consider agranulocytic angina as a syndrome, rather than a definite clinical entity.

As to the differential diagnosis, Rosenthal and Harris (32) have the following to say, " After the anemia develops, it becomes progressive and responds only temporarily to the usual therapy for secondary anemia. If the color index is relatively high, as it is in some cases, the leukemia may simulate pernicious anemia. The characteristic macrocytosis of pernicious anemia, however, is not observed, but the presence of the immature lymphocytes is indicative of the leukemic condition. All cases of chronic progressive anemia and splenomegaly require continued and careful study of the blood. Leucopenic leukemia or aleukemic leukemia may simulate splenic anemia, hemolytic icterus, subacute endocarditis, Goucher's disease, and thrombosis of the splenic vein. Here again, the presence of enormous numbers of lymphocytes or of some immature forms should point to the diagnosis of lymphatic leukemia. In rare instances the blood picture of aplastic anemia and of aleukemic lymphatic leukemia may be identical with respect to the profound anemia, thrombocytopenia, leukopenia, and relative lymphocytosis. In such cases the presence of splenomegaly or lymphadenopathy may indicate leukemia. In some cases a correct diagnosis can be made



only after a biopsy of the bone marrow which may reveal the lymphoid metaplasia of the rare medullary lymphatic leukemia as described by Fries.(45).

Bleeding from the mouth, nose, gums, may be an early symptom of the leukemias, particularly the acute types, and if careful analysis of the blood is not made, it is very confusing with purpura hemorrhagica. Splenectomy has been done in these cases due to the failure to make a good complete blood count.

Leukemia may sometimes be confused with other conditions giving generalized lymphadenopathy, such as Hodgkin's disease, non-specific lymphadenitis, or lymphosarcoma. However, the blood picture should differentiate these conditions. There has been considerable evidence in recent years that lymphatic leukemia and lymphosarcoma are only different stages in the same pathological process. Kato and Brunschwig (48), in a recent survey of the literature on this subject, find that Kneal (49), Young and Spalding (50), Hensel (51), Flashman (52), Cooke (53), and others have reported cases similar to the two they report, and with the same results and outcome. They summarize as follows: " Two cases are reported in which the patients when first seen had lymphosarcoma with normal blood picture; a short time later acute lymphatic leukemia developed, with a rapidly fatal termination. This is additional evidence in favor of the view that lymphatic leukemia and lymphosarcoma are stages of the same process. Roentgen therapy was instituted in both of these cases immediately after a diagnosis of lymphosarcoma was made, and

the question therefore arises as to whether or not this treatment induced the leukemic state."

Infectious mononucleosis (lymphocytosis or monocytosis) may be mistaken for leukemia. The clinical course of the disease is, however, usually typical of a benign condition with fever, sore throat, absence of anemia, and transient lymphocytosis or mononucleosis.

Lymphatic leukemia may even be confused with rheumatic fever in children. Sutton and Bosworth (54) cite a case in a girl of  $2\frac{1}{2}$  years of age in which painful swelling of the joints with cardiac symptoms was the only symptom found on two admissions over a period of  $3\frac{1}{2}$  months. Then, six months later she entered the hospital and died of a typical lymphatic leukemia. The blood count during the  $3\frac{1}{2}$  months was relatively normal. Cooke (5) lists rheumatic pains as the third most common symptom in acute lymphatic leukemia in children. Poynton and Lightwood (55) mention a case of theirs in which fleeting pains in the joints and swellings were noted for seven weeks before admission to the hospital, and the case had been called acute rheumatic fever. After she entered the hospital she rapidly became worse, and the blood count showed aleukemic lymphatic leukemia.

Karshner (56) mentions a case which so closely simulated acute osteomyelitis that an operation was performed finding no pathology. However, later X-ray showed changes and will be mentioned under "Pathology".

## PATHOLOGY

The pathological changes in chronic and acute lymphatic leukemia are, in general, the same. However, due to the relatively short duration of the acute form, the lymphatic infiltration of the various parts of the body are less extensive. The usual purpuric and hemorrhagic tendencies of the acute leukemias, while not usually observed during the greater part of the course of chronic type, do occur occasionally during the terminal stages. The gross pathology usually noted is a general enlargement of the lymph nodes, especially cervical, axillary, and inguinal, enlargement of the spleen, altho not as massive an enlargement as usually seen in myelogenous leukemia and an enlargement of the liver, and of course, the definite changes in the blood.

## LYMPH GLANDS:

Enlargement of the lymph nodes, excepting the blood picture, is probably the most constant symptom in lymphatic leukemia, and may usually be noticed by the naked eye. On section, the cut surface is smooth, homogenous, soft, greyish white or reddish grey in color with an occasional small hemorrhage. Histologically the gland may be scarcely recognizable because of the distortion of its normal architecture by the enormous numbers of infiltrating lymphocytes which tend to obscure the follicles and their germinal centers. The sinuses and capillaries if they can be made out at all, are seen to be dilated and filled with lymphocytes. The vessel walls are often sclerosed. Small lymphocytes predom-

inate in the chronic cases, but occasionally large lymphocytes are found. Lyday (24) and Wiel (59) report cases in which their patients died of lymphatic leukemia, but biopsy of cervical lymph glands before death showed typical tuberculous adenitis.

#### SPLEEN:

The enlarged spleen may show infarcts, and the Malpighian bodies are often unrecognizable. Histologically, the organ is simply a mass of lymphocytes, and in advanced cases may be recognizable as being spleen only by the presence of characteristic trabeculae. In cases of long duration, there is a tendency of proliferation of fibrous tissue between the venules. Often the capsule is thickened by a perisplenitis.

#### LIVER:

The liver shows fatty degeneration, and also infiltration with lymphocytes. " This is not a diffuse process, but is limited entirely to the periportal tissues." (60) This is a striking difference between lymphatic and myelogenous leukemia. The vessels are not markedly dilated, but contain numerous lymphocytes.

#### BONE MARROW:

Piney gives a good description of the bone marrow changes. (60) " The bone marrow is usually found to be more extensive than normal, and often resembles red-currant jelly; occasionally it is not possible to find any macroscopic change in the marrow, and indeed there may even

more uncommonly be apparant decrease in the amount."

Histologically, the changes are those of extreme lymphatic infiltration which, to a greater or lesser extent, replaces the myeloid tissues. " This irritation of the myeloid tissue by lymphocytes is no doubt the cause of the presence of immature cells of myeloid series which are found in almost all cases of lymphatic leukemia, altho in very small numbers."

#### THYMUS GLAND:

Piney (60) states that the thymus gland is almost always enlarged, sometimes to a very great degree, and may even infiltrate adjacent tissues in a tumor-like manner. The normal histological arrangement of the thymus is obliterated, and it is found to consist of a fairly evenly arranged mass of lymphocytes most of which are small. Involvement of the capsule by infiltration with lymphocytes is quite usual, and such a process may extend into the perithymic tissue. In contrast to Piney's description of thymic involvement, Margolis (22) states: " The thymus gland is rarely enlarged in lymphatic leukemia; the prominent tendency in this disease is in the involution of the organ. When thymic enlargement does occur in leukemia, it usually parallels the degree of infiltration of the other organs. Such enlargement of the thymus gland is not due to hyperplasia of the small thymic cells, but is due to infiltration by lymphocytes; the process is identical with that leading to infiltration of other non-lymphoid organs. A different histogenic source of the small thymic cells from that of the

blood lymphocytes may be inferred." Craver and McComb (23) say, "---tumifaction of the thymus in association with lymphatic leukemia, while rare, is a definite variant of that disease, and is probably the result of leukemic infiltration of the organ."

#### MOUTH AND THROAT:

There is not usually any specific pathology in the mouth and throat. Most of the hemorrhage seen occurring from the mucous membranes of the mouth, gums, throat, is merely due to the hemorrhagic diathesis of the disease, however, occasionally leukemic infiltration around the smaller blood vessels will cause their rupture, and necessarily, hemorrhage. Noma has been reported as has generalized sloughing of the mucous membranes of the mouth.

#### EYES:

Cohen (61) reports a case of orbital lymphoma of leukemic origin, and hemorrhages into the fundus are common in the acute cases. In the chronic cases, the fundus may occasionally show "retinitis leukemica", small white flecks with a red border, a peculiar type of hemorrhage, and blurring of the optic disc.

#### EARS:

Fioretti (quoted from Ordway and Gorham (3)) mentions a case of chronic lymphatic leukemia with otitis media and deafness. Histologic examination showed leukemic infiltration of the mucosa of the tympanic cavity.

#### LUNG:

There are no characteristic findings in the lungs.

However, chronic passive congestion is seen if the cardiac decompensation is present in a great enough degree. Pleural effusion may occur; possibly due to leukemic infiltration of the mediastinal lymph nodes.

#### HEART:

There are no changes specific of leukemia, but as anemia progresses, myocardial insufficiency may develop. Mitral insufficiency may be seen.

#### KIDNEY:

The main changes in the kidney are those of fatty degeneration, but it also may show grey linear markings due to infiltration of lymphocytes. The pelvis of the kidney may contain diffuse leukemic deposits which may be hemorrhages.

#### SEX ORGANS:

Priapism is a rare condition, and is caused by the also rare condition--leukemia, in 40% of cases. Mechanically, it is a persistent filling of the corpus cavernosum of the penis. The normal blood filling due to the normal stimulation sexual response is replaced by a modified blood of a high white cell content. In some cases this filling has been considered pus. The blood vessels of the cavernosa are thinned out, stretched widely, separated, and filled with the masses of leucocytes and many thrombi of white cells. Leukemia is also said to be the cause of priapism in the female, but I could find no further description of it. (62)

## BONE:

Karshner (56) reports six cases of lymphatic leukemia which all showed bone changes described by the attending roentgenologist as follows; "----revealed periosteal proliferation involving the upper end of the left ulna beneath which there was some destruction; finely porous destruction at the lower metaphysis of both bones of each forearm; periosteal proliferation about the upper end of the shaft of the left humerus with a large destructive lesion involving the underlying metaphysis. Finely porous destruction of the metaphysis of both humeri, of the ribs, of the bones of the pelvis and of the upper end of the femur was also noted."

Poynton and Lightwood (55) in their recent discussion of a case with bone manifestations report about the same findings as Karshner, notably, periosteal thickening, and bone destruction. The periosteal thickenings on histological examination showed typical lymphatic infiltration.

## GASTRO-INTESTINAL TRACT:

The pathology of the condition when involving the gastrointestinal tract, varies from slight swelling of the mucous membrane and lymph follicles to extensive hyperplasia of all the lymphoid tissue of the alimentary canal. When the stomach is enlarged to any appreciable extent, the mucosa is thrown into great folds, described as simulating cerebral convolutions. Polypoid formations are also often present. Ulcerations and involvement of the muscularis is not common. A survey made in 1904 by Wells and Maver (65) showed about



238 cases of leukemia which went to autopsy. The gastro-intestinal tract was involved to some extent in 34 of these. The stomach and intestines were involved in 13 of these. The stomach alone, in 7, and the intestine alone, in 15. (64) Boikan (63) reports a case in which the gastro-intestinal pathology was outstanding. " The stomach was enormously enlarged with huge convolutions on the inner surface, giving it a brain-like appearance. The small and large intestines were beset with huge plaques, and polyp-like masses. The microscopic examination of the stomach revealed an infiltration of the mucosa and submucosa by confluent lymphoid nodules. Slight regressive processes in the form of superficial ulcerations and hemorrhages were present." " In leukemia there exists no proportion between the symptoms arising from the gastro-intestinal tract and pathologic changes therein. Most extensive changes may be symptomless." Hemorrhages may be specific or non-specific, due to the hemorrhagic diathesis which accompanies the acute disease. Mead (64) reviewed a case in which the main symptoms were of a gastro-intestinal nature, and a preoperative diagnosis of "polyposis of the stomach" was made. The stomach was tremendously large and filled with tumor masses. All the regional lymph glands were also enlarged, and the intestines, especially the upper one third was punctated here and there with small tumors, both inside and outside the bowel. Biopsy showed lymphatic leukemia.

## CENTRAL NERVOUS SYSTEM:

In 1926 Fried (66) made an exhaustive survey of the literature and found only thirty cases of leukemia in which central nervous involvement was mentioned. He does not say which were lymphatic and which were myelogenous. He also reports a case of his own. He summarizes as follows:

" In the authors case, a patient with a subacute leukemic lymphadenosis died of apoplexy, and at necropsy numerous lymphomas and hemorrhages were found in the brain. Grave degenerative changes were found in the interstitial, parenchymatous and mesenchymal elements of the brain, more pronounced in the vicinity of the extravasated blood and also around the lymphomas. In the thirty cases gathered from the literature, lesions of the nervous system have been reported in the hemispheres in 12, in the cranial nerves in 8, and in the cord in 11 cases, in 8 of which spinal degenerations were observed in the absence of lymphomas, in many respects resembling those observed in pernicious anemia."

Diamond (67) states the brain changes as follows:

" The histologic changes may be circumscribed or diffuse, local or general. They may be divided into 1. leukemic infiltration of the meninges, cranial nerves, perineural spaces, and parenchyma of the brain, 2. degeneration of the ganglion cells and nerve fibers with rarefaction, and 3. reactive proliferative phenomena of the meninges, blood vessels and glia." I shall merely name some of the clinical pictures manifested by these changes in the brain described by

Diamond--diplegia, facial diplegia, paralysis of lateral eye muscle, and paraplegia. Critchley and Greenfield (70) in discussing the spinal cord changes in leukemia say that the commonest cause of paraplegia in leukemia results from a more or less extensive cellular infiltration of the spinal meninges.

Howell and Gough (68) report a case with facial diplegia of the Bell type in a boy of eleven years, and say further that, " Cerebral complications in leukemia usually take the form of gross hemorrhages, or large areas of infiltration in the cerebral hemispheres. These lesions are associated with suddenly developing paralysis or such symptoms as delirium, headache, and vertigo. Less commonly, local involvement of certain of the cranial nerves develops. Garvey and Lawrence (69) present one case of facial diplegia, and one case of facial monoplegia as a result of and caused by lymphatic leukemia. Both were typical leukemic cases, and autopsy showed perivascular infiltrations of lymphocytes, with a resulting weakening of the wall and hemorrhage.

" The seventh nerve nuclei cells showed marked alterations similar to those following injury to a peripheral nerve."

Hill (72) mentions a case of nasopharyngeal tumor of lymphoblastic origin giving intracranial increased pressure and papilledema. Cooke (5) reports a case of transverse myelitis in a child.. White (71) reports a case of combined sclerosis as caused by lymphatic leukemia.

## SKIN:

Skin manifestations of leukemia are many, including pruritis, prurigo, urticaria, bronzing, papules, vesicles, pustules, localized infiltration, nodules, tumors, petichia, hematomas, and leukemia cutis. All these eruptions except leukemia cutis are not peculiar to leukemia, but are characterized by unusual intensity when associated with leukemia.

Pruritis is intense and persistent both day and night.

Urticaria may be urticaria with the ordinary flat evanescent wheals; it may be papular; or papulovesicular. The eruption is kept up indefinitely by the recurrence of lesions, or by their persistence.

Prurigo may occur, and is characterized by an eruption of solid, small, round or conical pale papules or papulovesicles. Secondary infection often occurs when the tops are scratched off the papules.

Purpura may occur in leukemia as a discrete petichial eruption or as a diffuse areas of extravasation of blood into the skin. It occurs not only on the skin, but also upon the mucous membranes. The diffuse hemorrhage into the skin may be very extensive, one case described by Pusey (73) showing an extravasation of blood producing a mahogany-black discoloration of the skin of the entire head, face, and trunk down to the diaphragm.

Dermatitis exfoliativa. It is not known whether this is due to an intoxication of leukemia, or by true superficial infiltration of the skin. Clinically, it looks like all other

exfoliative dermatitis.

Herpes may occur.

MacKenna (74) reports a case with peculiar skin manifestations. There were lesions on the extensor surfaces of the legs which closely resembled hypertrophic lichen planus.

On the arms they simulated lichen rubra planus, except for the violaceous hue so characteristic of that disease.

Fleuroscopic examination showed leukemic infiltrations.

LEUKEMIA CUTIS is the true leukemic manifestation in the skin, and occurs in two forms. 1. circumscribed leukemia cutis, and 2. universal leukemia cutis. The circumscribed form manifests itself as flat patches of infiltration or as tumor-like masses. The lesions are brownish or dark red and semi-translucent. They are usually soft and elastic, but may be hard. They occur usually on the face, in about the same region as erysipelas. They do not ulcerate unless secondarily infected. The universal type is very rare, and is the picture of a persistent universal infiltrated chronic scaling dermatitis. Arndt describes the histological picture thus, "A continuous, diffuse, pure, lymphocytic infiltration of the upper two thirds of the derma, going down to the lower one third of the cutis propria and the subcutaneous tissue in the form of perivascular and periglandular cell collections." (73) Large lymphocytes predominate; mitoses are numerous.

It can readily be understood, after knowing something of the pathology of lymphatic leukemia, and especially the

wide distribution of those changes in the body why the diagnosis of the disease may be so easily mistaken. This makes one realize the importance of making routine blood counts. The symptomatology may be so different from that of a typical leukemia, that one perhaps would not think of making a blood count, which would reveal the true nature of the disease at hand.

### PROGNOSIS

Both chronic and acute lymphatic leukemia are fatal diseases. Rarely, cases have been reported as cured (57), but most authors consider these cases as those of mistaken diagnosis; not accepting the diagnosis of leukemia as correct, if the patient recovers. Of all types of leukemia, the prognosis as to length of life after the onset of the disease, is best in chronic lymphatic leukemia. They have been known to live fourteen years after the symptoms first appeared. This, however is very unusual; most of the patients dying in from two to three years. Acute lymphatic leukemia is rapidly fatal, most patients dying within a week or two after the onset of symptoms, but some may live four or five months. Weisman says, (58) " The best index as to the severity of the process is obtained by an analysis of the number of young lymphocytes as revealed by the criteria determined from the study of the normal maturation of these cells."

## TREATMENT

At the present time, the treatment of leukemia, due to our limited knowledge of its etiology, is purely symptomatic. The ends to be accomplished are 1. improvement of the general condition and affording comfort by rest, diet, and sedatives, and 2. increase the strength and efficiency by blood transfusions and roentgentherapy. Many other forms of therapy have been suggested and used, among which are malarial inoculations, embryonic extracts, sulfur, arsenic, benzol, and splenectomy, but the two treatments which still remain in favor are blood transfusion and roentgenotherapy.

Benzol or benzene has long been used as a treatment of leukemia. Ordway (75) in 1916 outlined the method of using benzol, stating that at that time the method of administering it was almost uniform. " Capsules, in certain instances coated with salol, containing 0.5 gm. of benzol, are given with equal parts of olive oil to diminish the irritating local effect. Two such capsules are given at first, increasing until 10, that is, 5.0 gms. per day are administered. They should be taken immediately after meals, and never during meals, and it is important that the patient be kept in the hospital during such treatment. It may take 10 days to 3 weeks before the effect on the blood is observed." Billings (78) in 1913 reported five cases of leukemia in which only one was the lymphatic type which showed phenomenal

improvement under benzol therapy. The white count went down, the spleen and lymph glands became smaller, and the patients felt much better. Pancoast (76) in 1917 mentions four cases of leukemia treated with benzol. He failed to state the type of leukemia. In one case, benzol improved symptoms for three months. In two, it did no good. The fourth responded well to the first treatment, returned to his work and felt quite well for two years. He then had a relapse. A second series of treatments were begun, to which he responded nicely at first, but died soon after. Aubertin (77) reiterates that "In leukemia, benzene cannot be expected to cure, but the prolonged remissions are of great gain. Benzene treatment requires close supervision." Rosenthal and Harris (32) cannot say a good word for benzol therapy, and can see no place for the drug in the treatment of lymphatic leukemia.

Before Senn initiated roentgenotherapy in cases of leukemia, drugs had to be relied upon, and one of the most popular for a time was arsenic, used first by Bromwell. Now it is considered to be of practically no value, but is often used between courses of x-ray or radium. Spiedel (79) says the best way to administer arsenic is to begin with doses of not less than 5 min. three times a day for the first two days, preferably in orange juice immediately after meals. On the third and fourth days, 6 min. three times a day, and then increase until 10 min. are given three times a day. Then increase 1 min. a day until toxic symptoms occur.



Friedgood (80) says, "Lugols solution has a definite effect, especially in chronic lymphatic leukemia in relieving some of the symptoms associated with a high basal metabolic rate."

Izaacs (18) says the administration of iron and liver is of some value at times as a means to combat the anemia.

Malarial therapy is apparently of little value.

Gamble (81) reports poor results with malarial therapy. The total white count was lowered for three days, but then rose to where it was before treatment. Also, the red cell count rapidly went down, he thinks, due to hemolysis. Bini (82) in 1926 points out that a favorable influence of accidental malarial infection on leukemia has been reported twice in the literature.

Pearce (57) presents a case of a girl, age 8, who developed a severe acute aleukemic lymphatic leukemia. The blood count before treatment was as follows: leucocytes 9,600, hemoglobin 12%, erythrocytes 860,000, polys 7, lymphocytes 87. She was very sick with a moderate fever, edema of the ankles and legs, loud blowing systolic murmur, and anorexia. She was given an intramuscular injection into the gluteus muscle, of 5.0 cc. of a 40% albumen-free solution of hog spleen. Two days later 1.0 cc. of a 20% solution of liver extract was given. These injections were repeated two and four days later respectively. She improved, and two further injections of hog spleen and liver extract were given at two day intervals until ten doses had been given. She then was put

on one teaspoonful of liver extract twice a day, which was still being used when the case was reported. Following the intramuscular injections the blood count showed that the hemaglobin content was 88%, the red cells numbered 6,330,000, the white count was 16,200 with 55 polys and 41 lymphocytes. Five months later, the child was going to school, feeling fine, with a normal blood count. Gonce, Middleton, Bradley, and Nichols, after extensive experimentation with various splenic extracts have the following to say, " From these rather inadequate data, it may be concluded that the spleen extracts prepared by the methods herein described, were without therapeutic effect in the cases of lymphatic leukemia studied." (83)

Blood transfusions are still used often in lymphatic leukemia, and are undoubtedly of great temporary value. Their effectiveness is of course only transient; the blood count and general condition being improved for a few days, only to drop back again.

Ordway (75) in 1916 reported several cases in which radium was helpful after x-ray and benzol had failed to give any improvement. Improvement was noted in the spleen and lymph glands, in the white cell count and differential, and in the general condition of the patients. Rosenthal and Harris (32) state that radium, in the form of surface application or packs is used only in the event that roentgenotherapy is not available, or in patients who cannot be moved from their homes.

It is quite generally accepted at the present time that our best means of treating the leukemias is by the roentgen ray. There are many times effected long remissions, up to three or four years or more with the use of the x-ray. It must be kept in mind, however, that this treatment, like all the rest, is only symptomatic, and can by no means be spoken of as a cure.

Fox and Farley (84) in 1923 summarized the effects of irradiation on lymphoid tissue as follows: " Mild doses playing upon lymphatic tissue cause low-grade hyperplasia in cords and follicles while protracted or repeated exposures are followed by a diminution of small mononuclears. After the reduction of the normal lymphocytes from repeated radiation, larger cells develop resembling the normal lymphoblasts in appearance. They seem to act as lymphoblasts. These cells are somewhat resistant to the action of x-rays. If irradiation of normal lymph nodes be not too prolonged, for example to the extent of fibrous tissue stimulation, normal architecture and histogenesis will probably return. The stage of degeneration in lymphatic tissue is demonstrated by swollen or vacuolated cells, in pyknotic or fragmented nuclei and by " chromatin dust". Reactive phenomena take the form of an increase of the lymphoblasts noted above, a prominence of endothelial cells, and later, connective tissue overgrowth; both of the latter two seem stimulated by x-ray directly or by the degeneration products of cellular death. The endothelial cells, because of evidence of phag-

ocytosis in them, and because they seem to multiply during treatment have been thought to participate not only in the removal of cellular debris, but actually to affect the destruction of lymphocytes."

X-ray was first instituted as a treatment for leukemia by Senn (85) in 1903. It was not said what type of leukemia Senn's first case was, and a differential blood count was not reported, but I believe his case was of the myelogenous type. The spleen decreased from a size large enough to fill almost the entire abdomen, to near normal size; the patient felt much better; and no recurrence had been noted when the article was written. Since Senn's first use of the x-ray, its use has gradually met with great favor in the treatment of leukemia. Boardman (86) in 1916 states that the x-rays have produced improvement in from 20% to 50% of the patients, that is, 50% to 80% of all cases are refractory.

Izaacs (87) says, " Roentgen irradiation stimulates primitive lymphoblasts to rapid reproduction. Small lymphocytes are stimulated to finish their life history and they then die or are excreted. The latent period between the exposure to irradiation and the elimination of the leucocytes represents the period of maturation and development of the individual cells to senility." Izaacs (18) at another time says, " The roentgen rays, then stimulate certain cells in some stages to grow old and die of senility or be eliminated, while in other stages the cells are made to grow more rapidly. The first effect is desirable; the second undesirable.

Therefore, it is best to not expose a patient to x-ray too often, especially as the results become less effective with each succeeding treatment. X-ray should be used only when 1. there are pressure symptoms from enlarged glands or spleen, 2. when there is a high leucocytosis associated with high basal metabolic rate, and 3. when anemia is progressing rapidly. Izaacs (88) also noted an increase in the red blood cells in cases of leukemia treated with x-ray, but many other authors disagree, saying that the red cells are decreased.

The technique of radiotherapy is discussed by McAlpin, Golden, and Edsall.(89) " In lymphatic leukemia, the cervical, axillary and inguinal areas are treated with medium voltage rays (approximately 125-135 kv., peak), 3 mm. aluminum filter and a 10 inch target skin distance. Two thirds to three fourths of an erythema dose is applied over one area at a sitting. The most prominent nodes are selected for the first treatment. The patient returns once or twice a week. Usually once. If the mediastial or abdominal nodes are involved, high voltage rays, (equivalent of 200 kv. peak) are used with 0.5 mm. copper filter and 50 cm. target skin distance, one-eighth of an erythema dose being applied at one sitting." Rosenthal and Harris (32) have the same views. The long bones are irradiated in some cases. Some authors even advocate irradiation of the entire body. Orton (90) thoroughly agrees as to the small dosage. Reynolds (92) has the following to say, " I always begin treatment with small doses at about 80 kv., usually 1 erythema dose filtered

with  $\frac{1}{2}$  mm. aluminum, and not until this irradiation has ceased to have any appreciable effect do I resort to higher potentials." Furth and Kabakjian (91) working with mice, exposed the entire mouse to gamma rays, in a metal cage, and found that the animals which were suffering from lymphatic leukemia lived 19 to 26 days longer than those that did not receive the x-rays.

Horder (93) says that irradiation of lymph glands will reduce them in size, but the blood picture is not changed. Irradiation of the spleen gives better results. Irradiation of the bones may be helpful, and in some cases where these methods are ceasing to be effective, x-ray of the entire body may be of some value. Horder also says that the state of the red cells and the hemoglobin must be watched in order to control dosage. "They have even greater importance than the state of the white cells." Izaacs (87) in regard to the dosage says, "As to the actual dosage, in general it may be said that the larger the effective dose given at one time (within the course of three or four days) the quicker will be the response on the part of the blood cells." Tomanek (95) irradiates patients, refractory to roentgen rays, with permanent application of radium for one to three weeks.

Knott and Watt (94) in trying to determine some way to control dosage of x-ray--to know when to give more, when to cut down, and what initial dose to give; devised what is known as their "phagocytic test". In this test, the technique which need not be given here, the number of ac-

tively phagocytic leucocytes present in the peripheral blood is measured. Their phagocytic properties varies directly with their maturity, so a case in which the cells are more mature offers the best chance of aid by x-ray. The number of actively phagocytic leucocytes also varies in direct proportion with the chronicity of the disease.

Minot and Izaacs (96) conclude from a study of their results with and without irradiation that the length of the life of the leukemic patient is not markedly influenced by irradiation, but that he is able to live, while he does live, in greater comfort and freedom from symptoms.

#### CONCLUSIONS

1. Lymphatic leukemia is a disease of the blood forming organs, and is a relatively rare condition.
2. The etiology is unknown.
3. The four main features of the disease are, (a) general lymphadenopathy, (b) splenomegaly, (c) enlarged liver, and (d) relative and usually absolute lymphocytosis.
4. Pathological changes due to infiltration of the tissues by lymphocytes have been noticed in nearly every part of the body.
5. Lymphatic leukemia has always a fatal termination.
6. Blood transfusions and small doses of roentgenotherapy offer the most symptomatic relief.

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